Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site #1124, Dr. Ankur Sarkar This site enrolled 9 subjects. PPD made several unsuccessful attempts to collect the data on these 9 subjects. On May 17, 2002, Nadine Grathe, SM inquired by email whether we should leave these patients in the database or delete them and just keep the information somewhere else so we can comment on them in the FSR. Following is a summary of attempts to retrieve data from Dr. Sarkar's site. • On 11MAR02, Site Management CRA contacted the site in an attempt to collect outstanding CRFs. The receptionist indicated that Dr. Sarkar would be out of the country until 08APR02. • On 14MAR02, Field Monitor conducted a visit at this site in an attempt to collect outstanding CRFs. The PI was still out of the country. The site personnel didn't know anything about the study and were unable to provide assistance regarding the 9 subjects. The site personnel located the Study Reference Manual, and the Field Monitor noted that both the Subject ID Log and the Randomization Log had not been completed. The Field Monitor was unable to identify the 9 subjects in order to review charts. Only CRF pages for Subject 1 had been partially completed (pages 1-2). The Field Monitor couldn't confirm that subjects had signed an informed consent form. The Field Monitor met with the hospital administrator, Stephen Gullarte, during the visit to discuss these issues. Mr. Gullarte indicated that Dr. Sarkar was an employee of the hospital since the hospital owns the clinic. Mr. Gullarte indicated that if Dr. Sarkar was conducting research it was in breech of his employment contract with the hospital. • On 14MAR02, Teresa Dunlap and Cathy Tropman had a conference call with Mr. Gullarte to discuss the issue. Mr. Gullarte again explained that he was extremely surprised to learn that Dr. Sarkar had been conducting a research study at the clinic. Mr. Gullarte was cooperative; however, he explained that neither he nor the clinic staff could provide assistance because they didn't know anything about the research study. • On 18APR02, Field Monitor conducted a visit in an attempt to collect CRFs for the 9 subjects enrolled. Prior to this visit, Teresa Dunlap, Sr. Project Manager, had scheduled the visit with Dr. Sarkar personally. Dr. Sarkar indicated that he would be available for the visit at 11 a.m. Upon arrival, the receptionist gave the Field Monitor the remaining lab kits, the remaining investigational product, incomplete randomization log and incomplete drug dispensation log. The Field Monitor was informed that Dr. Sarkar didn't have time to meet with him, and that all study materials had been provided to the Field Monitor. The Field monitor was unable to verify informed consent for the 9 subjects and was unable to collect CRFs. • On 18APR02, Melinda Edwards, Project Manager at PPD, contacted the site to discuss	This issue was discussed with the GCP QA upper management and inclusion in the database and transparent disclosure of reason for missing CRF data in the CSR was recommended. Documented correspondence with these sites needs to be clear on investigator responsibilities and sponsor expectations. In addition to CSR disclosure, it will be necessary to pursue agency notification (per 312.56b) if we are unable to access site documents and/or harvest CRFs. This notification is pending availability and review of prior correspondence with the sites to confirm appropriate actions have been taken (and documented) to secure compliance. On 5/21/02, Melinda Edwards, Project Manager at PPD faxed the following information to Aventis GCP-QA: • Follow up letter for visit 1 • Confirmation letter, IMVR, and FU letter for visit 2 • IMVR, and FU letter for visit 2 • Four page fax sent to site on 2/28/02 • Two page fax sent to site	In email dated 8/18/ 2002 from Paul Bryers it is noted that: 1. Paul/Mike to call Dr Thomas, DSI to -inform Dr Thomas of the 2 investigators/sites in Study 3014 that have refused to provide source documentation or completed CRFs -inform Dr Thomas how we intend to deal with these sites in the Study Report for 3014,. -propose to Dr Thomas documentation that Aventis will submit to him. 2. Paul to call Judit Milstein, PM DAIDPs to let Division know of this issue and let them know we are dealing with Dr Thomas on this issue. 3. Mike to provide package for submission to Dr Thomas - Summary for each site and Supporting documents as agreed with Dr Thomas. 4. Paul to generate cover letter to accompany package to Dr Thomas - review required by Mike and Steve. In email dated 7/1/2002 from Paul Bryers it is noted that the following w ording was noted in the CSR: "During monitoring visits at two sites (1124 and 2340), source documents were either not available or were incomplete, or CRFs were not available. The 10 subjects from these two sites were

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
the importance of verifying consent and collecting CRFs for the 9 subjects enrolled. Melinda spoke to the director of the clinic, Anita, who again explained that the site personnel had no information regarding the research study or subjects enrolled. Anita indicated that Dr. Sarkar was at the hospital and was not available for the monitoring visit. • On 20APR02, Teresa Dunlap sent an email to Dr. Sarkar requesting his cooperation with the collection of data from the site. Teresa indicated that a monitor would be returning to the site to collect the data. • On 22APR02, Teresa Dunlap spoke to Mr. Gullarte. Mr. Gullarte was upset and felt that his staff was being harassed by PPD. Teresa informed Mr. Gullarte that PPD had scheduled another visit with Dr. Sarkar in order to retrieve data. • On 23APR02, Field Monitor conducted a visit in an attempt to collect CRFs for the 9 subjects enrolled. Prior to this visit, Teresa Dunlap, Sr. Project Manager, had scheduled the visit with Dr. Sarkar personally. Dr. Sarkar was only available for a couple of minutes during the visit, then left the clinic. The field monitor collected CRF pages for subjects 001 and 002; however, the CRFs were incomplete. The field monitor was not able to confirm that the 9 subjects had signed consent forms.		excluded from the study analyses."
Site #2340, Dr. Richard Barber The site enrolled 2 subjects, but neither subject received study drug. We never received CRFs for the 2 enrolled subjects. Subject 002 was randomized in the IVRS, but has a PCN allergy. When the PI was instructed that this was a protocol violation because the subject didn't meet inclusion/exclusion criteria, the PI indicated that he no longer wanted to participate in the TREAT study. • At least 4 phone messages following this incident were left for the PI in January, and he never returned the calls. • At least 5 phone messages were left for the PI in February, and he never returned the calls. • An on-site monitoring visit was scheduled for February, but the PI informed the monitor that if he showed up at the site, the site would not allow him to conduct a visit. • The PI indicated that he was going to return his payment to PPD. (To date, PPD has not received a returned check, but the check has not been deposited either). • At least 4 phone messages were left for the PI in March, but the PI has not returned messages. On May 17, 2002, Nadine Grethe, SM inquired by email whether we should leave these patients in	This issue was discussed with the GCP QA upper management and inclusion in the database and transparent disclosure of reason for missing CRF data in the CSR was recommended. Documented correspondence with these sites needs to be clear on investigator responsibilities and sponsor expectations. In addition to CSR disclosure, it will be necessary to pursue agency notification (per 312.56b) if we are unable to access site documents and/or harvest CRFs. This notification is pending availability and review of prior correspondence with the sites to confirm appropriate actions have been taken (and documented) to secure compliance. On 5/21/02, Melinda Edwards, Project Manager at PPD faxed the following information to Aventis GCP-QA:	In email dated 6/18/ 2002 from Paul Bryers it is noted that: 1. Paul/Mike to call Dr Thomas, DSI to -Inform Dr Thomas of the 2 investigators/sites in Study 3014 that have refused to provide source documentation or completed CRFs -Inform Dr Thomas how we intend to deal with these sites in the Study Report for 3014 -propose to Dr Thomas documentation that Aventis will submit to him. 2. Paul to call Judit Milstein, PM DAIDPs to let Division know of this issue and let them know we are dealing with Dr Thomas on this issue.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
the database or delete them and just keep the information somewhere else so we can comment on them in the FSR.	• Phone contact reports for the period 1/14/02 to 5/16/02 • Faxes dated 2/1/02, 2/4/02 and, 3/16/02 3/27/02 On 5/22/02, Nadine Grethe has provided GCP QA with a copy of the letter dated 4/10/02. On the fax a possibility of notifying the FDA and the IRB is noted.	3. Mike to provide package for submission to Dr Thomas - Summary for each site and Supporting documents as agreed with Dr Thomas. 4. Paul to generate cover letter to accompany package to Dr Thomas - review required by Mike and Steve. In email dated 7/1/2002 from Paul Bryers it is noted that the following wording was noted in the CSR: "During monitoring visits at two sites (1124 and 2340), source documents were either not available or were incomplete, or CRFs were not available. The 10 subjects from these two sites were excluded from the study analyses."

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site # 0469, Dr. Vincent Sghiatti On May 24, 2002, GCP-QA was informed by an email from Melinda Edwards, Project Manager at PPD of issues at the site that was recently monitored. A monitoring visit was conducted at Vincent Sghiatti's site in California on 8-12APR02. This site was a high-enrolling site and also had low reporting of adverse events. PPD tried several times to schedule/conduct a visit at this prior to the scheduled date of 8-12APR02 (PPD had a monitor in CA a few weeks prior to this visit and the site refused to let the monitor conduct the scheduled visit). During the visit on 8-12APR02, it was noted that the site had numerous issues. The PI also was not present during the visit, but the study coordinator, Ester Zetino, was present during the visit. Here is a summary of the major findings at this site: • drug accountability log was not completed at all • there were dosing discrepancies noted by reviewing the source documents • the site had low reporting of adverse events, and the monitor noted several unreported adverse events during the visit • the study coordinator could not locate the remaining investigational product for drug return • PI didn't sign any of the ICFs (123 subjects) [however, the person obtaining consent and the subjects had signed the ICFs]. • No subjects signed the CA Bill of Rights (123 subjects) • ICFs were missing for subjects 076 and 123 • PI didn't sign any lab reports indicating that the reports had been reviewed Currently, the Site Management CRA is trying to resolve the outstanding issues with the site via phone contacts and faxes, but is having difficulty. One of the field monitors, Jill Moody, is trying to schedule a visit with the site to help with resolving all of these issues (she is trying to schedule the visit for the week of June 3).	These issues were discussed with Melinda Edwards, PM at PPD who confirmed that no doubt exists regarding the reliability of the data collected from this site, and no mispractice could be suspected. According to Melinda, the site was essentially "sloppy" although they had indicated that they have phase II-IV research experience. Melinda Edwards confirmed that the California Subjects Bill of Rights was not sent to the CA sites as an attachment to the ICF, but rather as a part of the binder which has resulted in a few sites not having the subjects sign the California Subjects Bill of Rights. Jill Moody, Sr. CRA at PPD will be conducting a Monitoring Visit at this site on June 3-4, 2002 and will resolve all outstanding issues. Further follow up action will be decided after receiving feedback from Jill Moody.	Jill Moody, Sr. CRA, PPD conducted the monitoring visit at this site on June 3-4, 2002. In email dated 6/6/02 from Jill Moody after she completed the monitoring visit it is noted that : No unreported AESIs or SAEs were noted during the visit on June 3rd and 4th. Dennis Geoff, staff member, completed DAL through subject 060 at the time of the visit. A MTF was prepared regarding the issue of PI did not sign the ICF for subjects Subjects 001 – 124. The CRA I instructed the SC to continue to have the PI resign and date the ICFs with the current date and to add a notation explaining the late entry. At the time of the visit subjects 007, 015, 041, 047, 049, 051, 109, and 112 have returned and dated their signature. The site was reminded to continue to attempt to have subjects return to the office to resign and date with a notation indicating the original date of consent. This notation was not present for the subjects who have already returned. SC confirmed that this memo has been faxed to the IRB. A confirmation page was not available. For the issue of Subjects 076 and 123 not having ICFs on file: Subject 076 has signed/date a new ICF. An ICF for subject 123 is still not present. The

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
		site confirmed that they are still trying to have the subject return. MTF to document this issue was generated and sent to PPD and IRB. 57 of the 124 subjects have returned to sign/date the Experimental Bill of Rights. The site was instructed to continue to have these subjects return to review, sign and date the CA Experimental Bill of Rights. MTF was completed and sent to PPD and IRB. For subjects 003, 007, 017, 018 and 109, source indicated subjects dispensed Ketek, IVR indicated Augmentin. Prior to visit a memo was sent to PPD confirming that subjects were dispensed Augmentin. The source documents were reviewed and the correction had been made to indicate that Augmentin was dispensed to the subjects. The DAL reflected that Augmentin was dispensed to these subjects (DAL was not complete for subject 109). For issue of Subjects 014, 027, 038, 106, 107, 118, 121, and 124: Subjects did not initial all or some of pates 1 – 5 of ICF. Subject 014 has initialed all pages of the ICF. The site was instructed to continue to attempt to have subjects return to initial the pages with a notation of the original date that the page was reviewed. A memo was generated and sent to PPD and IRB. The site confirmed that the PI has reviewed, signed and dated all lab reports.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site #1129, Dr. A. Kirkman-Campbell Anne Kirkman-Campbell, MD [Investigator No. 1129] is the highest enroller in the TREAT Study with 407 subjects enrolled. PPD CRAs Christiane Hammond and Jerry Ferguson monitored this site on November 29, 2001. The CRAs monitored three of the 65 subjects enrolled at the time of that visit. Ranjan Khosla (GCP-QA, Aventis) had conducted an audit at this site on January 17-18, 2002. At the time of the audit the site had enrolled 327 subjects. The auditor reviewed all 327 ICFs, the essential document binder, drug accountability and the charts of subjects 060, 080, 100, 140, 180, 191, 200, 220, 240, and 280. The Study Coordinator entering the date for the PI and/or the subjects on the ICFs; the PI entering the date for the person obtaining the consent and/or the subjects; partial compliance to the CFR 312.62 requirement that the case history of each individual shall document that informed consent was obtained prior to participation in the study; and other problems pertaining to informed consent were some of the significant issues. During the exit interview, the auditor confirmed that the PI and the Study Coordinator were not aware of the complete definition and reporting requirements of Adverse Events of Special Interest [AESI] and the Serious Adverse Events [SAEs]. The auditor subsequently requested the Clinical Team to conduct Source Data Verification [SDV] of more patients at this site and it was decided in the weekly team interaction meetings that PPD will send three CRAs to this site who will attempt to monitor 100 randomly selected subjects spread out among the 407 subjects enrolled. On the monitoring visit on February 18, 19 and 21, 2002 the three PPD CRAs Ann-Marie Cisneros, Elizabeth Heding and Stephanie Love monitored 36 subjects (Elizabeth Heding and Stephanie Love monitored only on February 18 and 19, 2002 and Ann-Marie Cisneros monitored on all three days). GCP-QA was informed by e-mail on February 27, 2002 by Jessica Lasley, Director TCC, PPD, about the observations of the CRAs of potential scientific misconduct discovered during the interim monitoring visit, which took place at the site of Dr. Anne Kirkman-Campbell [Investigator No. 1129] on February 18, 19 and 21, 2002 (the clinic was closed on February 20, 2002). First elements received reported that proper diagnosis of an appropriate medical condition to warrant study entry was lacking; medical charts were very limited; short time of randomization in the IVRS (large numbers of patients in a short increment of time and most occurred when the office was closed for lunch and not seeing patients); informed consent form anomalies including date modifications and patient signature inconsistencies; and a review of lab values for multiple patients appeared to be similar. At the time of the monitoring visit, Dr. Kirkman-Campbell site had enrolled 407 patients.	In accordance with the applicable Aventis Global Regulatory SOP GREGU-QAC-PR-01-01 "Scientific Misconduct and Fraud", a teleconference was organized on March 4, 2002 to review the case, and evaluate first investigations to be initiated. Recommendation was given to carefully follow up the implementation of the following actions: • W. Stager (Statistician, Aventis) wil perform a statistical analysis of the lab data from Covance to determine the likelihood of obtaining the observed numbers of matching lab samples by chance. • The Study Manager will ensure that a follow up letter is sent to the site asking for written explanation of the following issues by the site: ➢ A description of the informed consent process and an explanation of the issues observed. ➢ It is understood that the nature and extent of the disease state is not critical to this clinical trial mimicking normal practice but the PI should explain the source documentation practices followed by the site and clarify the issues observed in the monitoring visit. ➢ The randomization of subjects in blocks/ clusters within a short period of time is highly unusual. The site should explain the randomization process followed by them. ➢ Having reported very few Adverse Events (except for the five AESIs consisting of abnormal Liver Function Tests) for the 407 subjects enrolled is	In email dated 3/14/02, Bill Stager provided a Evaluation of blood samples collected by site 1129 in protocol 3014: *"The following report examines the pattern of laboratory evaluations obtained from blood samples drawn at site 1129 in protocol 3014. The objective of this analysis is to assess whether the distribution of values within a day are less variable at this site than predicted by the overall distribution and by the distribution at other high enrolling sites.* *The procedure used for this evaluation, based on a comparison of the variation laboratory values collected on the same day with the overall variation in the full data set. Analysis was carried out specifically for the variables ALT and total bilirubin which are related to liver function, a key objective of the trial, and for which the data are most complete. Data from days with at least two valid assays were used. For reference, the same analysis was carried out on the next two highest enrolling sites 1057 and 096 which have patient sample sizes approximately half that of 1129."* *"The findings show a smaller variation in values for blood samples collected on the same day than across days for sites 1129 and 096. For site 1129 the intra-day variation was greater than that seen with site 1057 and less than site 096 as*

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	highly unusual. What is the process at the site for obtaining and documenting Adverse Events from subjects? • Since the monitoring plan requires a monitoring of 25% patients and until now source data verification for only 49 of the 407 subjects has been performed [3 in the monitoring visit on November 29, 2001, 10 during the Clinical QA Audit on January 17-18, 2002, and 36 during the monitoring visit on February 18, 19 and 21, 2002] the possibility of a further monitoring visit will be explored. This is necessary to rule out the possibility of any unreported Adverse Events of Special Interest [AESIs]. • The answer will be obtained from the site to the question asked in the Audit Follow up letter dated January 21, 2002 about the total number of patients seen by the PI in the months of October, November and December 2001. • Documentation will be obtained from PPD about the training given to the site regarding the complete definition and reporting requirements of Adverse Events of Special Interest [AESI] and the Serious Adverse Events [SAEs]. • Based upon the statistical analysis of the lab data from Covance and the responses of the PI to the follow up letter, meeting will be held to decide future action. On 3/19/02, the follow up letter was sent to the site listing above issues. On 4/24/02, Melinda Edwards, Project Manager at PPD faxed the Memos to File to Aventis GCP-QA where the site had addressed the following issues: • Informed Consent Process • Source Document process	*determined by the variance ratios (1.58 vs 1.25 and 1.61 for ALT and 1.94 vs 1.36 and 2.28 for total bilirubin) with higher variance ratios indicating smaller intra-day variation compared to overall variation. A similar pattern is seen in higher intra-class correlations (0.040 vs 0.028 and 0.074 for ALT and 0.063 vs 0.040 and 0.145 for total bilirubin)."* *"Overall the results suggest a greater consistency in laboratory values within days than expected for site 1129. However a similar outcome was obtained in data from site 096. In addition the intra-class correlation estimates are small indicating a lack of a systematic pattern in the values within a day."* 1-5 April, 2002 third monitoring visit was conducted. Additional 70 patients were monitored. New deficiencies noted included enrolling patients with PCN/ERY allergy, new antibiotic therapy noted in some patients and DCF generated. The site has created MTFs to document all outstanding issues and has notified the IRB. The outstanding issue of Subject 249/VGS was resolved in the subsequent FDA Inspection Preparation visit on October 8-9, 2002 when it was observed that the initials of the subject matched their initials in the charts.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	• Randomization Process • Adverse event Reporting Process	Patricia S. Smith, FDA Investigator conducted an Inspection at this site on October 15-24, 2002. When she arrived at the site on October 24, 2002 for the close out discussion, she was accompanied by Robert West, Criminal Investigator, FDA. The PI contacted Aventis regarding guidance on the next steps to be followed. GCP QA and Clinical are working with the site to generate a 483 response.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site #0457, Dr. Roch Lefebre On Thursday, April 18, 2002, GCP-QA was forwarded an email by Nadine Grethe, SM from Jean Noone, Project Manager at PPD stating that Dr. Lefebre's business partner (Dr. Osborne) gave 2 patients TREAT study drug; 1 received 1 bottle of Ketek, the other 1 bottle of Augmentin.	The following recommendations were provided by GCP QA on 4/19/02: • The first element which is critical is to ensure that the patients who received the study drugs (and were not participating in the study) were correctly followed for SAFETY. We need to clearly know if any AE/SAE occurred. This needs to be documented in the investigator's letter and this should be part of the files with the memo/note describing the issue. Main concerns when this type of event occurs is related to patients' security / safety. Please make sure that this has been carefully handled and documented on-site. • Please have the site retrained about keeping the drug stored in a secure location with limited access. • The IRB needs to be informed about the non-study subjects receiving the study drugs. • The site should generate a Memo to document the issue and the corrective actions implemented. • A Monitoring Visit should be conducted at the earliest. A Monitoring Visit was conducted on 4/26/02.	On the meeting held on 5/31/2002 it was decided to request the site to inform the IRB. On Wed 06/05/2002, Ranjan Khosla sent the following email to Cathy Tropmann at PPD: *"I have followed up on the 5 recommendations provided to PPD about Site #0457, Dr. Roch Lefebre. I understand that a monitoring visit was performed at this site on 4/26/02. It is noted in the Phone Contact Report dated 5/1/02 the PI has not written the MTF and has not sent it to the IRB. Please follow up with the site and confirm that the site has generated a Memo to document the issue and the corrective actions implemented; and the IRB has been informed."*
Site # 0024, Dr. Jay Franklin On Wednesday, April 03, 2002, GCP-QA was informed by an email from Melinda Edwards, Project Manager at PPD of issues at the site that was recently monitored. Apparently all study records were accidentally destroyed as the result of termite spraying. The field monitor and site management CRA attempted to recreate some of the documents for the site (study binders, copies of CRFs and queries, copies of lab reports, etc). This site is a high-enrolling site (enrolled 16 subjects), and is not a research naive site (has Phase IV research experience).	The following recommendations were provided by GCP QA: 1. Missing or misplaced ICFs: All efforts must be produced by the site to collect copies of the double ICF left to the patient. If not possible contact with the patient should be documented and reason why	In email dated 6/25/02, Teresa Dunlap, PM at PPD informed that Monitoring visit was conducted at this site on 6/24/02. According to the CRA, Jill Moody all subjects have been identified but she could not review all of the charts. She did review source documents of subjects 001/S-C, 002/Z-G

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
• The monitor could not perform 100% SDV for most subjects because there were no office charts for a majority of the subjects. • There were no informed consent forms for subjects. The site was instructed to try and obtain copies of the consents from the patients. • 2 Subjects were under the age of 18 • One subject (016) is a Lost to Follow patient, and the site isn't sure who the patient is at this point.	not obtained documented as well. The main issue is obviously the missing ICFs and this is the priority in the corrective actions. 2. The site should document in a Memo to File the destruction/ discarding of the study binders, CRF's, signed ICF's, Covance laboratory supplies, and study drug dispensation. The site should inform the IRB about these issues. 3. As the CRFs are already in house we can make a copy for the site from the original to keep at site. 4. We can send them new study binders with copies of all their required documents included. 5. For the 2 Subjects who were under the age of 18 years, PPD should request the site to generate Memos to File and submit a copy to the IRB and to PPD. 6. For the subjects 001, 002, 003, 004, 005, 006, 007, 009, 010, 012, 014, 015 who are Women of Childbearing Potential [WOCBP], PPD should request the site to verify whether a pregnancy test was performed at visit one. If no documentation is present to confirm, then the site should generate Memos to File and submit a copy to the IRB and to PPD. 7. TRAINING: Please retrain the site about the proper informed consent procedure as noted in ICH GCP Guidelines section 4.8 and in the 21 CFR Part 50. Also retrain the site about proper source documentation practices as described in the ICH 1.51, 1.52 and 4.9. The site should also be retrained about keeping	[employee], 003/C-R [Study Coordinator], 004/C-K [employee], 006/MA, 008/JIP, 011/DJS, 013/J-M and 014/J-G. This site had randomized 16 subjects. On 4/17/02, the PI confirmed over the phone that he did not file a police report. PI provided the name and contact phone number of Jerry Utech at the Termite Spray company. PPD is following up. Teresa Dunlap, PM at PPD confirmed on 6/25/02, that till date PPD has not been able to obtain a copy of Termite spraying receipt or confirm that this work was performed as the contact person at the termite spray company has not returned any of the messages left by PPD. In email dated Wednesday, June 26, 2002 from Gerard Marini it is noted that: "Nadine, Following our yesterday's telephone discussion, I and Ranjan reviewed again the feedback obtained following the monitoring visit, which took place on Monday June 24. I also discussed this briefly with Mike for GCP-QA consensus. It was noted that the patients came back to the site to re-sign ICF (even if this was done with new GCP issues in terms of back dating, stamp use, etc.), and noted that all subjects could be identified (even if all charts were not reviewed ... and GCP-QA will pursue contact with PPD to ensure that the charts are effectively faxed and reviewed ...).

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	the study documents and investigational products in a secure location with limited access. Please document all the training provided to the site. 8. It is the opinion of GCP QA at Aventis that it is not a good practice for the Principal Investigators to enroll themselves or their staff members or close relatives. There are no particular objections to this type of enrollment as per GCP guidelines (at least this is not properly covered "in the text"), if all the rules regarding the patient free consent after receiving adequate information about the study are complied with. However, we recommend avoiding this type of recruitment as it is always difficult to demonstrate that this was managed properly and that no conflicts of interest occurred due to the particular relationship Investigator - Staff Member. There is also the issue with data confidentiality and access to those data by other staff members, including Sponsor's representatives during monitoring, etc. Please request the PI not to enroll her/his staff members or close relatives in this and future Aventis studies. It was requested that the CRA Lisa Gustofson provide us with further information about the destruction/ discarding of the study binders, CRF's, signed ICF's, Covance laboratory supplies, and study drug dispensation etc. at this site. Also requested that PPD should get a copy of the Termite sprayer invoice/receipt as proof that it was done	Those facts decrease the level of non-confidence from what could have been considered as potential misconduct to another level I would summarize as site with poor GCP compliance, including poor documentation practice. It appears then that data collected can be validated and then dispatched in the CSR, and this site managed as the others were handled in the CSR."

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site # 2557 Jeff McLeod, MD On Wednesday, March 06, 2002 9:59 AM GCP-QA was informed of the following problems at this site by email from Linda Karolak, CRA II, TREAT Study Team [her email listing the sequence of events is quoted directly]: "On March 4, it came to my attention by the PI, Dr. Jeff McLeod, (who is listed in our database as having No Research Experience), that he did not have any of the 30 subjects he randomized into the TREAT trial sign the IRB approved ICF. He claimed that he never received his IRB approval packet from Copernicus Group IRB. We have his Copernicus Group IRB approval documented on Dec. 4, 2001. Dr. McLeod has had numerous site management calls, but has never been very cooperative in listening to all that I had to convey in the call. He did have initial site management calls in December, shortly after he became active as a PI, and I have documented that we discussed the ICF process briefly on Dec. 27, 2001, so I was very surprised to hear this "bad news" on March 4. Dr. McLeod did say that he felt confident that he could call his subjects back to sign the IRB approved ICF. I emphasized to him at that time that there is to be NO BACK DATING.I told him that he must have them sign the current date. I faxed the Protocol Violation Memo To File to Dr. McLeod on Mar. 4, asking him to sign and date it, fax it back to PPD and to the Copernicus Group. I have not seen the signed Memo To File arrive back to me yet. I gave the PV worksheet to CRA Dana Dibling to have this PV added to the PV Tracker. I notified Copernicus Group about this on Mar. 4, and heard back by email from them on Mar. 5 that they faxed a copy of his IRB approved ICF to him. I had asked a contact person at Copernicus Group IRB for Federal Express tracking information regarding the IRB approval packet that went out to Dr. McLeod, assuming that it did, but I have not received any information from Copernicus Group about that. Dr. McLeod's site was to have been monitored on March 7 and 8 this week, and my Sr. CRA Mark Bedell talked with PM Jean Noone and Melinda Blanks about this on Mar. 4, and it was thought best to postpone the visit so that Dr. McLeod can contact his subject to sign the ICF. A copy of the IRB approved ICF had also been faxed to Dr. McLeod by me on Mar. 4. The Interim Monitoring Visit is now scheduled for March 28 and 29 (1 and 1/2 days). Dr. McLeod's CRFs have been sent to Quintiles, and he has been issued 3 payment checks...1) $1400 for subject randomization, 2)$500 for Holiday enrollment, and 3) $1600 for subject randomization. On March 5, I talked with Robert McCormick about this site. Robert told me that Dr. McLeod should not be given an IRB approved ICF to have his subjects sign now, but a copy of the ICF had already been faxed to Dr. McLeod. I told Robert that not sending the ICF was not the directive that I had received from project manaagement on March 4. Robert told me to have my project manager call him. I told PM Jean Noone about this, and PM Tamea Dunlap offered to speak to Robert McCormick."	After discussions with Gerard Marini, Head of GCP-QA NAOC, the following recommendations were provided to PPD by GCP-QA Aventis on Wed 03/06/2002 5:54 PM: 1. Please conduct the Interim Monitoring Visit at this site as soon as possible. This MUST NOT be held up until all subjects have signed the ICF in the current date. We need to demonstrate due diligence as soon as we are made aware of the problems. 2. Please send a letter to the site thanking them for "SPONTANEOUSLY REPORTING" this major deviation from ICH and FDA regulations, protocol and the Declaration of Helsinki. Remind the site that 21 CFR 50.20, 21 CFR 50.27 and ICH 4.8.8 require that no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. Please ask him what event triggered this "SPONTANEOUSLY REPORTING" by the site. Please request the site that all attempts must be made to demonstrate a documented evidence that the subjects had consented without doing any back dating. Please have the site request all subjects to sign the consent in the current date and the subjects	The monitoring visit was conducted at this site on 3/21/02 by Sonia Hambleton, Associate Project Manager, PPD. It is noted in the follow up letter dated 3/25/02 that "The GCP (Good Clinical Practices) deviations noted (and discussed) were documented in a memo to file during the visit." The follow up letter also notes that the site was requested to send a copy of the memos to the IRB. The memo to file dated 3/21/02 sent to PPD and IRB notes that subjects 001 to 030 were verbally consented prior to study enrollment. Reviewed entire consent. noted that at that time 21 CFR 50.20, a 50.27 and ICH 4.8.8 requirements were not met. In another similar memo dated 3/21/02 it is noted again that for subjects 004, 008, 009, 011, 006, and 010 there was backdating of signatures of the subjects by subjects/ site. Also noted is that subjects were verbally consented but at that at that time 21 CFR 50.20, and 50.27 and ICH 4.8.8 requirements were not met.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Noone about this, and PM Teresa Dunlap offered to speak to Robert McCormick."	should write a statement to the effect that I CONFIRM THAT I HAD CONSENTED ORALLY ON _____[Date of verbal consent]. 3. Please request the site to submit a Memo to File documenting the informed consent issues at this site to the Copernicus IRB. The site must send a copy of this MTF to PPD.	

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site # 1654 Marie Monticciolo, MD On Tuesday, March 05, 2002 2:25 PM GCP-QA was informed of the following issues [as noted by the field monitor, Julie Geyer, who conducted the visit on Feb 27-28, 2002 at this site] by email from Melinda Edwards, Project Manager, PPD: • "CRA is suspicious that the sub-investigator, Richard Monticciolo (husband to the PI), signed the subjects names on the consent forms. (One example is that one subject's name is Jessica but signed her name Jennifer.) • Many of the subjects' signatures were shaky. • Also, CRA found labs for two subjects that were close to identical. The results at visit 2 were quite significant from visit 1 results and they both had them (the lab values were just off by 1 or 2 points in comparing the two subjects). The one subject is 25 yr and the other is 53. • CRA noted that there were very few AE's found. • Finally, a lot of the subjects had the exact same vitals such as a temp of 99 degrees, pulse of 70, and BP of 120/80. • I am not sure if Marie Monticciolo is aware of what was going on, however, she is the one that was writing the vitals for these subjects. (The consent process as well as the majority of the labs were being done by Richard Monticciolo)."	After discussion with Gerard Marini, Head of GCP NA Operations Center about this site an email was sent to PPD on Wed 03/06/2002 6:35 PM with following recommendations: Please ensure that a follow up letter is sent to the site asking for written explanation of the following issues by the site: ➢ A description of the informed consent process and an explanation of the issues observed by the CRA. ➢ It is understood that the nature and extent of the disease state is not critical to this clinical trial mimicking normal practice. Please request the PI to explain the possible similarities in the vital signs [for the few subjects] and lab values [for two subjects] observed in the monitoring visit. ➢ Having reported very few Adverse Events for just 27 subjects enrolled is not highly unusual. However, please request the site to explain what is the process at the site for obtaining and documenting Adverse Events from subjects? The information provided does not necessitate a Clinical QA Audit at this site at the present time.	The PI wrote a MTF on April 5, 2002 that notes that: • Subject 012's first name is Jennifer G. and her staff had inadvertently provided the chart of Jessica G. to the CRA. • Many subjects have temperature of 99 and pulse of 70 and a BP of 120/80. This is quite common in usual care setting and is not age dependent. • Subject 021's visit 1 total bilirubin and ALT were the same values as subject 022 visit 1 total bilirubin and ALT, but the rest of their visit 1 lab tests and all their visit 2 lab tests were not the same. • When an AE was initially recognized the PI called the site management CRA. In another MTF dated 2/27/02 it is noted that: • Subjects 001-027 did not date their ICF. • Site will attempt to bring subjects back to initial and date their ICFs with a notation of the original date the ICF was signed.
Site # 2647 Dr Ana Perez and site of Dr Raul Gaona On Friday, February 15, 2002 we were informed of the following: PPD received a fax from an S.M.O. Pro-Research Group informing them that they had an FDA inspection of their facility from 2/4-6/02. On 2/6/02 they were issued a 483 siting failure to keep complete documentation to show that all staff have been informed on the requirements of the study, their role and responsibilities regarding the study as per the Pro-Research SOP- "Pre-Study Requirements." Dr Raul Gaona is one of the two PIs in TREAT. He has enrolled 13 subjects and had a monitoring visit	It was agreed that an experienced CRA from PPD would go and monitor both the sites in one visit. The CRA will review the ISFs including a 100% SDV of all enrolled subjects [14+8].	PPD CRA Janet Bjork monitored the site of Dr Raul Gaona on February 25, 2002. All 14 randomized subjects were monitored. No significant GCP issues were noted. PPD CRA Janet Bjork monitored the site of Dr Ana Perez on February 26, 2002. All the

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Raul Gaona is one of the two PIs in TREAT. He has enrolled 13 subjects and had a monitoring visit on 12/5/01. The second site affiliated to this SMO, site # 2647 Dr Ana Peraz has enrolled 8 subjects. No monitoring visit scheduled or performed till now at this site.		8 randomized subjects were monitored. No significant GCP issues were noted.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site # 0454 Dr. Ashok Shah Tuesday, February 12, 2002 we were informed of the following problems at this site: 1. PI dated the ICF for 18 patients and PI initialed all pages of the ICF for the patients: pts. 001-045, and 047-068 (67 pts.). 2. PI did not sign same day as patient: 21 pts. 3. Pt. signed ICF post randomization: 1 pt. 4. PI did not write the year of the date on the ICF (i.e. "1/25"): 10 pts. 5.Missing or misplaced ICF (PI will continue to look for): 1 pt. 6. Subject didn't write the year of the date on the ICF: 1 pt. 7. PI signed but did not date ICF: 1 pt. 8. ICF pages are not initialed: 1 pt. 9. PI printed all the patients' names for them on the ICF (26 pts.) 9. One other violation found was patient 004/DM did not have Visit 2 labs drawn as patient refused.	After discussions with Gerard Marini the following recommendations were provided to PPD on 2/13/02: 1. PI dated the ICF for 18 patients and PI initialed all pages of the ICF for the patients: pts. 001-045, 047-068 (67 pts.): 21 CRF 50.27 and ICH 4.8.8 require that prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. Please request the site to document in a Memo to File that the ICFs were dated by the PI and send a copy of this Memo to the IRB and to PPD. 2. PI did not sign same day as patient: 21 pts.: The ICF has a place for the subject to sign and date, for the person obtaining consent to sign and date and for the Principal Investigator [PI] to sign and date. Confirmed from the CRA that there is no Study Coordinator at this site and the PI had obtained the consent from the subjects. Please document in a memo to file and forward a copy to the IRB and PPD. 3. Pt. signed ICF post randomization: 1 pt.: Please document in a memo to file and forward a copy to the IRB and PPD. 4. PI did not write the year of the date on the ICF (i.e. "1/25"): 10 pts.: Please request the PI to sign and write the complete current date on the ICF and document in a memo to file and forward a copy to the IRB and PPD.	In email dated 2/13/02, Melinda Edwards, PM at PPD informed that: "Thank you for your recommendations. I will forward these to Kristin Bredehoft, the monitor, so that she can include them in the trip report and follow-up letter. We plan to do an on-site closeout visit at this site to confirm that all of these issues were indeed resolved." In the follow up letter to the IMV performed on 2/7/02 the recommendations provided by Aventis GCP-QA were listed out for the site to take corrective action. Another follow up IMV was performed on 3/18-19/02. The site has created a total of 12 MTFs addressing the issues identified and sent copies of the MTFs to PPD and IRB.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	5.Missing or misplaced ICF (PI will continue to look for): 1 pt.: All efforts must be produced by the site to collect copies of the double ICF left to the patient. If not possible contact with the patient should be documented and reason why not obtained documented as well. 6. Subject didn't write the year of the date on the ICF: 1 pt. : Please request the PI to have the subject resign and write the complete current date on the ICF and document in a memo to file and forward a copy to the IRB and PPD. 7. PI signed but did not date ICF: 1 pt. : Please request the PI to resign and write the complete current date on the ICF and document in a memo to file and forward a copy to the IRB and PPD. 8. ICF pages are not initialed: 1 pt.: Please request the PI to have the subject initial and write the complete current date on the ICF and document in a memo to file and forward a copy to the IRB and PPD. 9. PI printed all the patients' names for them on the ICF (26 pts.): Please retrain the PI to let the patients print their names and then to sign and date the ICFs. 10. One other violation found was patient 004/DM did not have Visit 2 labs drawn as patient refused. : Please request the site to document this protocol violation and report it to the IRB and PPD.	

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site # 1860 Dr William Knox On Monday, January 07, 2002, I was informed about the site #1860 of Dr William Knox. Dr Knox has assigned incorrect subject numbers, dispensed drug without calling the IVRS, and PPD were having difficulty talking to him about these issues. No interim monitoring visit had been performed.	After discussions with Gerard Marini, Head of GCP NA Operations Center we recommended that: 1. A Monitoring Visit must be scheduled at this site at the earliest. 2. The CRA should perform 100% Source Data Verification for the 7 subjects enrolled to assess whether the data is evaluable and accurate. 3. Please retrain the site - both by phone [Site Management CRA] and by the CRA performing the IMV. 4. If it cannot be assured that the site is following the protocol and GCP guidelines, the site's participation in the study should be terminated at the earliest.	In email dated January 09, 2002, Roxann Evans, PM at PPD informed that: "Melinda Edwards the PM for the monitoring team has been sent this e-mail to set up the monitoring visit." The monitoring visit was conducted on February 26, 2002 and 100% SDV was completed for 7 randomized subjects and for 1 early terminated subject. MTFs were generated on 2/26/02 to address identified GCP issues.
Site # 1622 Dr. William Terpstra On Tuesday, January 22, 2002 we were informed on the following problems at this site: 1. ICF had been altered in some way: A. For subjects 089, 092, 093, and 095-160 one of the phone numbers had been marked out with black marker B. For subjects 001-160 the ICF indicated that the subjects would not be receiving compensation; however, the PI was compensating subjects $35 if they completed the study. Subject that did not complete the study did not receive any compensation. 2. The PI was unaware of GCP guidelines and IRB procedures. When the CRA discussed these with the PI he was argumentative about complying with the guidelines and the IRB. The PI did not seem interested in learning about GCP guideline or in following the guidelines. 3. Over 20 protocol violations were documented with the ICFs (this is not including the previously mentioned PVs). For example, several ICFs were not dated by the PI and consenter, one of the ICFs could not be located, and several ICFs did not have corresponding signature dates	After discussions with Gerard Marini, Head of GCP NA Operations Center we recommended that: 1. Please close the IVRS to this site immediately so that no new subjects are enrolled before we have ensured that site has resolved all outstanding issues. 2. Please send a Certified Letter to the site requesting the site to create an action plan to resolve all outstanding issues. Please ensure that all issues are addressed in the Certified letter and the following recommendations provided to the site: A. For subjects 089, 092, 093, and 095-160 in whose ICFs one of the phone numbers had been marked out with black marker; the site should have	Subsequent to the 1/17-18/02 IMV a follow up IMV was performed on 2/26-28/02. In MTF dated 4/18/02 the site noted that subjects 001-160 signed version 10/30/01 of the ICF. Most subject consents were changed to remove a site phone number and compensation prior to signing. Subjects that completed the study received compensation. In another MTF dated 3/26/02 regarding this issue, the site has noted that subjects 001-160 signed the IRB approved ICF dated 10/30/01 indicating that they would be compensated for their participation in the

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
ICFs could not be located, and several ICFs did not have corresponding signature dates between the PI and subject. 3. A cursory look at CRFs and source documents indicated that many subjects had visit 1 but had not come back for visit.2. Usually one phone call was being made and no other follow up was made to have the subjects return to the office. 4. The CRA was only able to look at 3 subjects; however, 2 of the 3 were enrolled with allergies to beta-lactam antibiotics. When CRA discussed this with the PI he questioned this exclusion criteria and when CRA showed him the criteria in the protocol he indicated he wasn't aware of this until the CRA showed him. The PI continued to question this exclusion criteria. 5. CRFs and logs are not legible and they are incomplete. 6. The PI does not have a SC or SI assisting him with the study. He is doing all the work himself and with 160 subjects it appears to be too much. Of more concern, the PI does not seem interested in correcting or learning from these errors.	the subjects sign a new ICF with current date, generate a Memo to File and notify the IRB. B. For subjects 001-160 the ICF indicated that the subjects would not be receiving compensation; however, the PI was compensating subjects $35 if they completed the study. The PI is not required to pay the subjects as the IRB approved ICF does not require that. However if he wants to pay the subjects he should have a transparent process of paying all the subjects regardless of whether the subjects completed the study. This is to ensure that there is no element of coercion involved. C. Please remind the site to follow the protocol diligently. The site should document all protocol violations in Memos to File and report them to the IRB. D. The site need to document due diligence in having the subjects come in for visit 2 by making phone calls and if that fails then by sending Certified Letters to the subjects. E. TRAINING: Please retrain the site about the proper informed consent procedure as noted in ICH GCP Guidelines section 4.8 and in the 21 CFR Part 50. Also retrain the site about proper source documentation practices as described in the ICH 1.51, 1.52 and 4.9. Please document all the training provided to the site. Please reeducate the site about the protocol inclusion and	study, however, each subject that completed the study received $35 compensation. If the subject did not complete all 3 visits the subject received no compensation. In MTF dated 3/26/02 it is noted that subjects 089, 092, 093, and 095-160 signed the altered IRB approved ICF dated 10/30/01. On page 1 of the ICF, one of the phone numbers under contact information had been obliterated. This same phone number was not obliterated on page 3.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	exclusion criteria. F. Please request the site to complete the CRFs and logs in a timely manner. 3. Please ensure that the site creates and implements an action plan to resolve the QA issues and please assess compliance in a future monitoring visit. If the site is found to be compliant in the next monitoring visit, then they should be allowed to enroll more subjects. If the site does not comply to the above mentioned recommendations, please close the site.	

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site 0881, Dr. Andrew Garner On Friday 01/18/2002 we were informed on the following problems at this site [Site has enrolled 86 subjects]: 1. 17 subjects had been enrolled prior to the revised consent. These subjects signed the revised consent and back dated the consent. The study coordinator, Cindy Seeley stated that they 'threw out' the original consents. 2. The PI signed the revised consent and photo copied each consent with his signature. The investigator had not dated many consents. 3. There were four consents missing. 4. Two consents had not been signed or dated by the subjects. 5. The PI is subject 071. 6. The PI stated to me that he was unaware of using source documents." Where is that mentioned in the protocol" There were some subjects that had source documentation, but the CRA got the feeling from the study co that there were many subjects that she saw for visit 2 and she did not complete a progress note. 7. One subject allergic to PNC, E-myacin, Tetracycline, and Biaxin.	After discussions with Gerard Marini, Head of GCP NA Operations Center we recommended that: 1. All efforts need to be made to retrieve the FOUR missing consents ... or have the patients come back to re-sign BUT no back dating. ALL deviations in the informed consent process, including dating practices ... missing consents, will need to be carefully described in file notes and endorsed/validated by the investigator. 2. Original signatures and dates from the investigator (at the time the patient consent was obtained) must be the only practice at the site. This needs to be reinforced to the PI. 3. Ensure that original patient charts are utilized to record source data if no site specific worksheets are utilized. Patient chart is usual medical practice ... if none exists, this site should not have been opened!!!! 4. TRAINING: Please retrain the site about the proper informed consent procedure as noted in ICH GCP Guidelines section 4.8 and in the 21 CFR Part 50. Also retrain the site about proper source documentation practices as described in the ICH 1.51, 1.52 and 4.9. Please document all the training provided to the site. 5. The PI should stop his participation in the	Subsequently, an audit was performed at this site on March 27 - 28, 2002. The site making changes to the "payment for participation" section of the IRB approved ICF; the site throwing away the ICFs for subjects 001 to 017; in several instances the person obtaining consent dating the ICF several days after the subject and sometimes earlier than the subject; use of photocopy of the PIs signature; and other problems pertaining to informed consent and protocol adherence were the significant issues that required corrective action. The final responses to the audit findings were provided on June 07, 2002 and the audit was closed on June 28, 2002.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	trial as a subject at the earliest. He should generate a Memo to File to document this and inform PPD and IRB. 6. Investigator's agreement must be obtained as related to his willingness to comply with this action plan to fill the gap with regulatory compliance. 7. If no immediate action is taken by the site to address these issues (re-monitoring is necessary to assess this ... rapidly) ... this site must be terminated and notified as such. We further recommend that a letter be sent to the site (with acknowledgement of receipt) providing him with all these elements ... letting him know about the actions, his required commitment and outcomes if no action is taken immediately.	

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site # 2344, Dr. Thorpe On Thursday, January 17, 2002 we were informed of the following problems at this site: Site 2344, Dr. Thorpe, in CA received his study drug Dec 4 and someone in this large practice he shares with other physicians put the drug with the office supply of 'pharmaceutical products' (we are assuming samples). We have been attempting to contact him weekly since he received his drug but with limited success. He is never available to speak to the CRA. One of the other physicians in the practice handed out a bottle of Ketek to one of their patients. When Dr. Thorpe learned of this, they immediately contacted the patient to discontinue the Ketek and return the bottle to the office, which he has not done. The patient did say he quit taking it.	After discussing the issues at this site with Gerard Marini, Head of GCP NA Operations Center we recommended that: 1. The first element which is critical is to ensure that the patient who received Ketek (and was not participating in the study) was correctly followed for SAFETY. We need to clearly know if any AE/SAE occurred. This needs to be documented in the investigator's letter and this should be part of the files with the memo/note describing the issue. Main concerns when this type of event occurs is related to patients' security / safety. Please make sure that this has been carefully handled and documented on-site. 2. Please have the site retrained about keeping the drug stored in a secure location with limited access. 3. The IRB needs to be informed about the non study subject receiving the study drug. 4. The site should generate a Memo to document the issue and the corrective actions implemented. 5. An Interim Monitoring Visit should be conducted at the earliest. Please note: Similar problem occurred at site 0206 where Augmentin was dispensed to a non-study patient. Same recommendations were provided when this issue was raised in the Team Interaction Meeting on January 23, 2002.	In MTF dated 4/30/02 it is noted that: "One bottle of Ketek was dispensed in error to a non-study subject by another physician. The subject was contacted and returned for proper treatment but the subject never returned the bottle of Ketek. This issue is also documented in another MTF dated 4/16/02. A follow up monitoring visit was conducted a this site on 4/16/02.
Site # 1630 Dr. Wendy Weiss	A Meeting was held on January 18, 2002 to discuss the GCP issues at the site of Dr. Wendy	Subsequently, this site was audited on April 04-05, 2002. The site making changes to the

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
On Friday, January 11, 2002 we were informed of the following problems at this site: During an interim monitoring visit at Dr. Wendy Weiss' site, site # 1630, it was discovered that the site had altered the IRB Approved Informed Consent. They changed the subject compensation from $75.00 to $50.00, using white out, made copies, and had the subjects sign the altered informed consent. Seventeen subjects were enrolled under using this altered informed consent. The traveling monitor alerted the site manager, stating that the PI said she was informed by The Copernicus Group that it was okay to do this. Dr. Weiss does not recall with whom she spoke with at Copernicus. PPD had the site write a memo to file stating what they did, and to inform the IRB. They also faxed in a revised IRB Questionnaire requesting a new ICF to reflect the new compensation amount, which was forwarded to the IRB.	Weiss and the following recommendations were agreed upon: 1. The IRB was notified, and this issue was documented on site. The Patient Informed Consent Form was revised and is being reviewed at the Central IRB level (The Copernicus Group) for approval. Waiting elements for confirmation, the enrollment at this site was stopped till further notice. In the light of the explanation collected, the enrollment can start again when the new IRB approved consent form is made available All patients will be re-consented when the newly IRB approved consent form is made available. 2. Verify list of sites participating in the study to check whether the audit visit can be combined with another site audit in Florida.	"payment for participation" section of the IRB approved ICF; the person obtaining consent dating the ICF several days after the subject; the person obtaining consent dating the ICF for the subject; and other problems pertaining to informed consent and protocol adherence were significant issues that required corrective action. Final Response Date was June 07, 2002 and the audit was closed on July 3, 2002.

Summary Table of GCP Issues
Telithromycin Respiratory Effectiveness Assessment Trial (TREAT) Protocol: HMR3647A/ 3014

GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site #2259 Dr. Samuel Stone On 1/31/02, Heidi Dunaway informed of the observations of Scott Scarola, CRA and her at Site #2259 Dr. Samual Stone, Chester, SC: 1. All 24 consents had something wrong with them: correction fluid over signatures; #010 only printed her name, she never signed/dated the consent (Scott brought a copy in-house of this one); #024 was randomized while the PI was getting consent but never consented the pt. due to intolerance to Biaxin. So there is a randomization # for #024, but no consent. Some subjects did not date their signatures and some did not initial all pages. 2. Source docs were non-existent. The coordinator said the dictation was about 2 months behind and that the PI does have the study information in the dictations. 3. Drug discrepancy. According to what we had (IVR and drug log) there were 2 Ketek bottles missing. They did not have the Fisher packing slips available. 4. Labs were not signed/dated. It looks like no labs are done at Visit 1 and blood draws are done at Visit 2 with Visit 1 lab kits.	After discussing the issues at this site with Gerard Marini, Head of GCP NA Operations Center we recommended that: 1. Please send a Certified Letter to the site requesting the site to create an action plan to resolve all outstanding issues. Please ensure that all issues are addressed in the Certified letter and the following recommendations provided to the site: A. For subjects in whose ICFs correction fluid was used over signature; the site should have the subjects sign a new ICF with current date, generate a Memo to File and notify the IRB. PREVIOUS VERSIONS SHOULD BE KEPT ON FILE AS WELL. B. For subject #010 who only printed her name, [she never signed/dated the consent] please request the site to have the subject sign the ICF in a current date, document in a Memo to File and notify the IRB. C. Please retrain the site to assess lab reports to assess clinical significance. Please remind the site to follow the protocol diligently. The site should document all protocol violations in Memos to File and report them to the IRB. D. For subject #24, please document in a Memo to File that the subject was randomized before signing the consent and the subject ultimately did not sign the ICF. Please inform the IRB. E. For subjects who did not date or initial the ICF, please have the subjects initial/ date in the current date, document in a Memo to File	Subsequently, this site was audited on February 7 - 8, 2002. At this site there were several problems pertaining to informed consent that were significant issues that required corrective action. One subject (010) has not signed the informed consent, and another subject (024) was randomised before obtaining consent and this subject had subsequently refused to participate in the study. The Clinic Nurse, Annette McDaniel who obtained consent from all subjects randomised the subjects in the IVRS while the subjects were reading the consent and had not yet signed the consent. She also entered the date for the PI on the ICFs. Final Response Date was March 22, 2002 and the audit was closed on June 13, 2002.

Summary Table of GCP Issues
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GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
	and notify the IRB. F. TRAINING: Please retrain the site about the proper informed consent procedure as noted in ICH GCP Guidelines section 4.8 and in the 21 CFR Part 50. Also retrain the site about proper source documentation practices as described in the ICH 1.51, 1.52 and 4.9. Please document all the training provided to the site. G. Please request the site to complete the CRFs and logs in a timely manner. H. Please request the site to document the two missing Ketek bottles in a Memo to File and to inform the IRB 2. Please ensure that the site creates and implements an action plan to resolve the QA issues and please assess compliance in a future monitoring visit.	

Summary Table of GCP Issues
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GCP-QA Issues Noted	Recommendations provided by GCP-QA NAOC/ Corrective Actions	Comments
Site 3294 Dr Jean-Claude Bourque On 1/3-/02, Nadine Grethe, SM forwarded an email from Roxann Evans at PPD listing the following issue: "Site #3294 Dr Jean-Claude Bourque called today and said the nurse left the TREAT supplies out in the office last night and their cleaning staff has discarded their study binders, CRF's, signed ICF's, Covance laboratory supplies, and unused study drug. Thus far they had enrolled 2 subjects both sinusitis. Okay to close this site and not send any more drug? We have requested the PI document what happened and provide detailed information to the IRB. Have requested visit 2 kits from Covance so the specimens can be drawn."	After discussing the issues at this site with Gerard Marini, Head of GCP NA Operations Center we recommended that: 1. All efforts must be produced by the site to collect copies of the double ICF left to the patients. If not possible contact with the patients should be documented and reason why not obtained documented as well. 2. The site should document in a Memo to File the discarding by the cleaning staff of the study binders, CRF's, signed ICF's, Covance laboratory supplies, and unused study drug. The site should inform the IRB about these issues. 3. If the CRFs were already sent in house we can make a copy for the site from the original to keep at site. And if they have not completed them yet, they can be completed now as apparently the source documents still exist. 4. We can send them new study binders with copies of all their required documents included. 5. The site should be retrained about keeping the study documents and investigational products in a secure location with limited access.	The site was instructed to stop enrolling subjects after subject 002. In MTFs faxed by the site to PPD on 2/1/02, and 2/6/02, the site had noted the discarding by the cleaning staff of the study binders, CRF's, signed ICF's, Covance laboratory supplies, and unused study drug. A follow up monitoring visit was conducted at this site on March 7, 2002. At the time of the visit the site had randomized 2 subjects. The follow up letter dated 3/18/02 notes that the CRA monitored the source documents and CRFs for both the subjects. Also noted in the follow up letter that the initial ICFs for both the subjects were not present.